REMARKS

Claims 1, 4-10 and 14 are pending. Changes to the claims are shown in the Appendix entitled "MARKED UP VERSION TO SHOW CHANGES MADE." A copy of the pending claims is attached for the Examiner's convenience. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

Objection under 35 U.S.C. 132

Claim 14 is objected to because the Examiner states that it introduces new matter into the disclosure. Applicant respectfully disagrees.

Claim 14 is directed to a method of treatment as in claim 1 wherein the cellular proliferative disease is a solid tumor. The specification provides support for solid tumor in Example 1. Example 1 describes treatment of mice with solid tumors using the claimed methods. The tumors are measured using a caliper, which would not be possible if they were not solid tumors. See page 7, lines 6-7. Applicant reminds the Examiner that the subject matter of a claim need not be described literally. M.P.E.P 2163.02. Applicant respectfully submits that the claim has adequate support and requests that the rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1, 4-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett et al. (U.S. Pat. No. 6,103,487). Applicant respectfully traverses.

Barnett teaches "partial esters derived from fatty acids and a hexitol ..." or "partial esters derived from fatty acids and hexitol anhydrides ...." Barnett does not teach the use of dianhydrogalactitol. Barnett does not teach that such partial esters can modulate a proliferative

disease or that the partial esters are provided in amounts sufficient to modulate a cellular proliferative disease. Barnett also does not teach a method as in claim 10 wherein the disease modulation is greater than modulation by the antiproliferative agent alone.

The claims are directed to methods of treatment of a host with a cellular proliferative disease. The methods comprise contacting the host with a composition consisting essentially of a pharmaceutically acceptable dianhydrogalactitol or analog thereof and a pharmaceutically acceptable antiproliferative agent. The dianhydrogalactitol or analog thereof and antiproliferative agent each are provided in an amount sufficient to modulate the cellular proliferative disease. The antiproliferative agent is selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes.

Claims 4-6 recite that the antiproliferative agent is an intercalating agent, a metal coordination complex, and cisplatin, respectively. Claims 7-9 recite that the dianhydrogalactitol or analog thereof may be administered before, during or after the administration of the antiproliferative agent, respectively. Claim 10 recites that the modulation of the disease with the composition is greater than the modulation by the antiproliferative agent alone.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must demonstrate three criteria. First, the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; second, the prior art must provide one of ordinary skill with a reasonable expectation of success; and finally, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. M.P.E.P. § 2143.

Without admitting the propriety of the rejection, Applicant has amended the claims. Applicant submits that the amended claims are clearly nonobvious over Barnett et al. First, Barnett et al. do not provide any suggestion to modify its disclosure to arrive at the claimed invention. Second, Barnett et al. do not provide a reasonable expectation of success of arriving at the claimed invention. Third, Barnett et al. do not teach all elements of the claimed invention. Applicant respectfully requests that the rejection be withdrawn.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis (U.S. Pat. No. 4,797,388, "Francis") further in view of Levin et al. (Cancer Chemother. Pharmacol. 8:125-31 (1982), "Levin"). Applicant respectfully traverses.

Francis teaches pharmaceutical compositions containing galactitol as a carrier for a therapeutic anti-tumor agent. The anti-tumor agent may be cisplatin. Francis further teaches that use of galactitol enhances stability of the therapeutic agent and allows faster reconstitution in water. Francis does not teach the use of dianhydrogalactitol.

Levin teaches that the antitumor activity of hexitol epoxides may be enhanced by drug combination therapies. Levin further teaches that the combination of dianhydrogalactitol and BCNU in treating IC glioma 26 (brain neoplasm) was curative in 85-100% of animals while treatment with either DAG or BCNU alone gave limited survival. Levin does not teach the use of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors or metal coordination complexes

The claims are discussed above.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must demonstrate a suggestion or motivation in the prior art to modify or combine the teachings of the

references to arrive at the claimed invention. Further, the prior art must provide one of ordinary skill with a reasonable expectation of success. Finally, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. M.P.E.P. § 2143.

Francis does not teach or suggest the use of dianhydrogalactitol or an analog thereof, nor that a dianhydrogalactitol or analog thereof modulates a cellular proliferative disease. Nor does Francis teach or suggest a method wherein the disease modulation is greater than modulation by the antiproliferative agent alone, as recited in claim 10.

Levin teaches the use of BCNU, an alkylating agent. Levin does not teach or suggest a method wherein the antiproliferative agent is an antimetabolite, a structural protein agent, an agent that affects protein synthesis, an antibiotic, a hormone antagonist, an intercalating agent, a topoisomerase inhibitor or a metal coordination complexes, as recited in the amended claim. Nor does Levin teach or suggest a method wherein the disease modulation is greater than modulation by the antiproliferative agent alone, as recited in claim 10.

To the extent that the Examiner may be relying on an "obvious to try" theory of obviousness, Applicants remind the Examiner that a rejection based on an "obvious to try" criterion is not proper under 35 U.S.C. § 103. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See also *The Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990). "An 'obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *The Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1928 (CAFC 1990).

In the present case, Levin teaches merely that DAG combined with BCNU enhances the effect seen by either agent alone in treating a brain neoplasm. Although the reference suggests

that further combination therapies may be useful, it fails to disclose the claimed drug combinations. Thus, it merely operates as an invitation to experiment further.

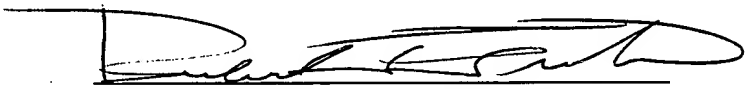
Francis does not cure the defects of Levin. First, Francis teaches the use of galactitol, not the use of dianhydrogalactitol or an analog thereof. Additionally, Francis uses galactitol as an excipient and does not teach the use galactitol as an active agent that can itself modulate a cellular proliferative disease. Applicant submits that because Francis deals with an excipient rather than an active agent, it provides no relevant motivation or teaching with regard to Levin. One skilled in the art would not be motivated by either art reference to modify the combination taught by Levin to obtain the claimed invention.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Applicants respectfully request that the Examiner call the undersigned attorney.

Respectfully submitted,

DORSEY & WHITNEY LLP



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MARKED UP VERSION TO SHOW CHANGES MADE

1. (Twice Amended) A method of treatment of a host with a cellular proliferative disease, comprising contacting said host with a composition consisting essentially of a pharmaceutically acceptable dianhydrogalactitol or an analog thereof, [hexitol] and a[n] pharmaceutically acceptable antiproliferative agent, each in an amount sufficient to modulate said cellular proliferative disease, wherein said antiproliferative agent is selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes.

4. (Twice Amended) The method according to claim 1 wherein said antiproliferative agent [comprises] is an intercalating agent.

5. (Twice Amended) The method according to claim 1 wherein said antiproliferative agent [comprises] is a metal coordination complex.

6. (Twice Amended) The method according to claim 1 wherein said antiproliferative agent [comprises] is cisplatin.

7. (Amended) A method according to claim 1 wherein said dianhydrogalactitol or analog thereof [hexitol] is administered before the administration of said antiproliferative agent.

8. (Amended) A method according to claim 1 when said dianhydrogalactitol or analog thereof [hexitol] is administered during the administration of said antiproliferative agent.

9. (Amended) A method according to claim 1 wherein said dianhydrogalactitol or analog thereof [hexitol] is administered after the administration of said antiproliferative agent.

PENDING CLAIMS

1. (Twice Amended) A method of treatment of a host with a cellular proliferative disease, comprising contacting said host with a composition consisting essentially of a pharmaceutically acceptable dianhydrogalactitol or analog thereof, and a pharmaceutically acceptable antiproliferative agent, each in an amount sufficient to modulate said cellular proliferative disease, wherein said antiproliferative agent is selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes.

4. (Twice Amended) The method according to claim 1 wherein said antiproliferative agent is an intercalating agent.

5. (Twice Amended) The method according to claim 1 wherein said antiproliferative agent is a metal coordination complex.

6. (Twice Amended) The method according to claim 1 wherein said antiproliferative agent is cisplatin.

7. (Amended) A method according to claim 1 wherein said dianhydrogalactitol or analog thereof is administered before the administration of said antiproliferative agent.

8. (Amended) A method according to claim 1 when said dianhydrogalactitol or analog thereof is administered during the administration of said antiproliferative agent.

9. (Amended) A method according to claim 1 wherein said dianhydrogalactitol or analog thereof is administered after the administration of said antiproliferative agent.

10. The method of claim 1 wherein the modulation of said disease with said composition is greater than that for said antiproliferative agent alone.

14. A method according to claim 1 wherein said cellular proliferative disease is a solid tumor.